Dichloromethane (CASRN 75-09-2)

0070

Dichloromethane; CASRN 75-09-2

Health assessment information on a chemical substance is included in IRIS only after a comprehensive review of chronic toxicity data by U.S. EPA health scientists from several Program Offices and the Office of Research and Development. The summaries presented in Sections I and II represent a consensus reached in the review process. Background information and explanations of the methods used to derive the values given in IRIS are provided in the Background Documents.

STATUS OF DATA FOR Dichloromethane

File First On-Line 01/31/1987

Category (section)	Status	Last Revised
Oral RfD Assessment (I.A.)	on-line	03/01/1988
Inhalation RfC Assessment (I.B.)	no data	09/01/1991
Carcinogenicity Assessment (II.)	on-line	02/01/1995

_I. Chronic Health Hazard Assessments for Noncarcinogenic Effects

_I.A. Reference Dose for Chronic Oral Exposure (RfD)

Substance Name -- Dichloromethane
CASRN -- 75-09-2
Primary Synonym -- Methylene Chloride
Last Revised -- 03/01/1988

The oral Reference Dose (RfD) is based on the assumption that thresholds exist for certain toxic effects such as cellular necrosis. It is expressed in units of mg/kg-day. In general, the RfD is an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. Please refer to the Background Document for an elaboration of these concepts. RfDs can also be derived for the noncarcinogenic health effects of substances that are also carcinogens. Therefore, it is essential to refer to other sources of information concerning the carcinogenicity of this substance. If the U.S. EPA has evaluated this substance for potential human carcinogenicity, a summary of that evaluation will be contained in Section II of this file.

__I.A.1. Oral RfD Summary

Critical Effect	Experimental Doses*	UF	MF	RfD
Liver toxicity 2-Year Rat Drinking Water Bioassay National Coffee Association, 1982	NOAEL: 5.85 and 6.47 mg/kg/day for males and females, respectively LOAEL: 52.58 and 58.32 mg/kg/day for males and females, respectively	100	1	6E-2 mg/kg/day

*Conversion Factors: Doses reflect actual values and not nominal ones.

__I.A.2. Principal and Supporting Studies (Oral RfD)

National Coffee Association. 1982. 24-Month chronic toxicity and oncogenicity study of methylene chloride in rats. Final Report. Prepared by Hazleton Laboratories America, Inc., Vienna, VA. (Unpublished)

The chosen study appears to have been very well conducted, with 85 rats/ sex at each of four nominal dose groups (i.e., 5, 50, 125 and 250 mg/kg/day) for 2 years. A high-dose recovery group of 25 rats/sex, as well as two control groups of 85 and 50 rats/sex, was also tested. Many effects were monitored. Treatment related histological alterations of the liver were evident at nominal doses of 50 mg/kg/day or higher. The low nominal dose of 5 mg/kg/day was a NOAEL.

The supporting database is limited. A NOAEL of 87 mg/cu.m was reported in one inhalation study (Haun et al., 1972). [The equivalent oral dose is about 28 mg/kg bw/day (i.e., 87 mg/cu.m x 0.5 x 0.223 cu.m/day/0.35 kg; these exposure values are for rats).]

__I.A.3. Uncertainty and Modifying Factors (Oral RfD)

UF -- (10a x 10h) The 100-fold factor accounts for both the expected intra- and interspecies variability to the toxicity of this chemical in lieu of specific data.

MF -- None

__I.A.4. Additional Studies/Comments (Oral RfD)

None.

__I.A.5. Confidence in the Oral RfD

Study -- High
Database -- Medium
RfD -- Medium

The study is given a high confidence rating because a large number of animals of both sexes were tested in four dose groups, with a large number of controls. Many effects were monitored and a dose-related increase in severity was observed. The database is rated medium to low because only a few studies support the NOAEL. Medium confidence in the RfD follows.

__I.A.6. EPA Documentation and Review of the Oral RfD

Source Document -- U.S. EPA, 1985

Other EPA Documentation -- None

Agency Work Group Review -- 06/24/1985, 07/08/1985, 11/06/1985

Verification Date -- 11/06/1985

Screening-Level Literature Review Findings -- A screening-level review conducted by an EPA contractor of the more recent toxicology literature pertinent to the RfD for Dichloromethane conducted in September 2002 did not identify any critical new studies. IRIS users who know of important new studies may provide that information to the IRIS Hotline at hotline.iris@epa.gov or (202)566-1676.

__I.A.7. EPA Contacts (Oral RfD)

Please contact the IRIS Hotline for all questions concerning this assessment or IRIS, in general, at (202)566-1676 (phone), (202)566-1749 (FAX) or hotline.iris@epa.gov (internet address).

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_I.B. Reference Concentration for Chronic Inhalation Exposure (RfC)

Substance Name -- Dichloromethane
CASRN -- 75-09-2
Primary Synonym -- Methylene Chloride

Not available at this time.

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_II. Carcinogenicity Assessment for Lifetime Exposure

Substance Name -- Dichloromethane
CASRN -- 75-09-2
Primary Synonym -- Methylene Chloride
Last Revised -- 02/01/1995

Section II provides information on three aspects of the carcinogenic assessment for the substance in question; the weight-of-evidence judgment of the likelihood that the substance is a human carcinogen, and quantitative estimates of risk from oral exposure and from inhalation exposure. The quantitative risk estimates are presented in three ways. The slope factor is the result of application of a low-dose extrapolation procedure and is presented as the risk per (mg/kg)/day. The unit risk is the quantitative estimate in terms of either risk per ug/L drinking water or risk per ug/cu.m air breathed. The third form in which risk is presented is a drinking water or air concentration providing cancer risks of 1 in 10,000, 1 in 100,000 or 1 in 1,000,000. The rationale and methods used to develop the carcinogenicity information in IRIS are described in The Risk Assessment Guidelines of 1986 (EPA/600/8-87/045) and in the IRIS Background Document. IRIS summaries developed since the publication of EPA's more recent Proposed Guidelines for Carcinogen Risk Assessment also utilize those Guidelines where indicated (Federal Register 61(79):17960-18011, April 23, 1996). Users are referred to Section I of this IRIS file for information on long-term toxic effects other than carcinogenicity.

_II.A. Evidence for Human Carcinogenicity

__II.A.1. Weight-of-Evidence Characterization

Classification --B2; probable human carcinogen

Basis -- Based on inadequate human data and sufficient evidence of carcinogenicity in animals; increased incidence of hepatocellular neoplasms and alveolar/bronchiolar neoplasms in male and female mice, and increased incidence of benign mammary tumors in both sexes of rats, salivary gland sarcomas in male rats and leukemia in female rats. This classification is supported by some positive genotoxicity data, although results in mammalian systems are generally negative.

__II.A.2. Human Carcinogenicity Data

Inadequate. Neither of two studies of chemical factory workers exposed to dichloromethane showed an excess of cancers (Ott et al., 1983; Friedlander et al., 1978; Hearne and Friedlander, 1981). The Ott et al. (1983) study was designed to examine cardiovascular effects, and consequently the study period was too short to allow for latency of site-specific cancers. In the Friedlander et al. (1978) study, exposures were low, but the data provided some suggestion of an increased incidence of pancreatic tumors. This study was recently updated to include a larger cohort, followed through 1984, and an investigation of possible confounding factors (Hearne et al., 1986, 1987). A nonsignificant excess in pancreatic cancer deaths was observed, which was interpreted by EPA (1987a) as neither clear evidence of carcinogenicity in humans, nor evidence of noncarcinogenicity. An update of the Ott et al. (1983) study, based on longer follow-up, indicated possible elevation of liver and biliary tract cancers (TSCA section 8(e) submission no. 8eHQ-0198-0772 FLWP et seq., 1989).

__II.A.3. Animal Carcinogenicity Data

Sufficient. Dichloromethane administered in the drinking water induced a significant increase in combined hepatocellular carcinoma and neoplastic nodules in female F344 rats and a nonsignificant increase in combined hepatocellular carcinoma and neoplastic nodules in male B6C3F1 mice (NCA, 1982, 1983). Two inhalation studies with dichloromethane have shown an increased incidence of benign mammary tumors in both sexes of Sprague-Dawley (Burek et al., 1984) and F344 (NTP, 1986) rats. Male Sprague-Dawley rats had increased salivary gland sarcoma (Burek et al., 1984) and female F344 rats had increased leukemia incidence (NTP, 1986). Both sexes of B6C3F1 mice developed liver and lung tumors after dichloromethane treatment (NTP, 1986).

In a 2-year study by the National Coffee Association (1982, 1983), groups of 85 F344 rats/sex/dose received 5, 50, 125, or 250 (mg/kg)/day of dichloromethane in the drinking water. Control groups consisted of 135 rats/sex. In female rats the incidence of combined hepatocellular carcinoma and neoplastic nodules was statistically significantly increased in the 50 and 250 mg/kg dose groups when compared with matched controls (0/134, 1/85, 4/83, 1/85, and 6/85 in the five dose groups 0, 5, 50, 125, and 250 (mg/kg)/day, respectively). The incidence of hepatocellular carcinoma alone was not significantly increased (0/134, 0/85, 2/83, 0/85, 2/85). The combined incidence of hepatocellular carinoma and neoplastic nodules in controls and the 4 dose groups (472 rats: 4 with carcinoma and 8 with neoplastic nodules) was similar to that for historical controls (419 rats; 5 with carcinoma, 19 with neoplastic nodules). Male rats showed no increase in liver tumors.

In the same National Coffee Association study (1982, 1983), B6C3F1 mice received 0, 60, 125, 185, or 250 (mg/kg)/day of dichloromethane in drinking water. Treatment groups consisted of 50 female mice and 200, 100, 100, and 125 male mice (low to high dose). One hundred females and 125 males served as controls. Male mice had an increased incidence of combined neoplastic nodules and hepatocellular carcinoma (24/125, 51/200, 30/100, 31/99, 35/125). The increase was not dose-related, but the pairwise comparisons for the two mid- dose groups were reported to be statistically significant (U.S. EPA, 1985a). The hepatocellular carcinoma incidence alone for male mice (which was about 55 to 65% of the total) was not significantly elevated. Female mice did not have increased liver tumor incidence. The EPA (1985b) regarded this study as suggestive but not conclusive evidence for carcinogenicity of dichloromethane.

A gavage bioassay of dichloromethane conducted by NTP (1982) has not been published because of high mortality, much of which was attributed to gavage accidents.

Inhalation exposure of 107 to 109 Syrian hamsters/sex/dose to 0, 500, 1500, or 3500 ppm of dichloromethane for 6 hours/day, 5 days/week for 2 years did not induce neoplasia (Burek et al., 1984). Sprague-Dawley rats (129/sex/ dose) were exposed under the same conditions. Female rats administered the highest dose experienced significantly reduced survival from 18-24 months. Female rats showed a dose-related increase in the average number of benign mammary tumors per rat (1.7, 2.3, 2.6, 3.0), although the numbers of rats with tumors were not significantly increased. A similar response was observed in male rats, but to a lesser degree. In the male rats there was a statistically significant positive trend in the incidence of sarcomas of the salivary gland (1/93, 0/94, 5/91, 11/88); the incidence was significantly elevated at the high dose. There is a question as to whether these doses reached the MTD, particularly in the hamsters and the male rats. In another study (Dow Chemical Co., 1982), 90 Sprague-Dawley rats/sex were exposed by inhalation to 0, 50, 200, or 500 ppm dichloromethane for 20 months (male) or 24 months (female). No salivary tumors were observed, but there was an exposure-related increase in the total number of benign mammary tumors in female rats, although the increase was not statistically significant in any individual exposure group.

Groups of 50 each male and female F344/N rats and B6C3F1 mice were exposed to dichloromethane by inhalation, 6 hours/day, 5 days/week for 2 years (NTP, 1986). Exposure concentrations were 0, 1000, 2000, or 4000 ppm for rats and 0, 2000, or 4000 ppm for mice. Survival of male rats was low; however, this apparently was not treatment-related. Survival was decreased in a treatment- related fashion for male and female mice and female rats. Mammary adenomas and fibroadenomas were significantly increased in male and female rats after survival adjustment, as were mononuclear cell leukemias in female rats. Among treated mice of both sexes there were significantly increased incidences of hepatocellular adenomas and carcinomas, and of alveolarbronchiolar adenomas and carcinomas, by life table tests. Adenomas and carcinomas were significantly increased alone as well as in combination. In addition, there were significant dose-related increases in the number of lung tumors per animal multiplicity in both sexes of mice.

Two inhalation assays using dogs, rabbits, guinea pigs, and rats showed no tumors, but were not conducted for the lifetime of the animals (Heppel et al., 1944; MacEwen et al., 1972). Theiss et al., (1977) injected Strain A male mice intraperitoneally with 0, 160, 400, or 800 mg/kg of dichloromethane 16 to 17 times, over 5 to 6 weeks. Survival of the animals was poor. The animals remaining 24 weeks after the first treatment were killed and examined for lung tumors; pulmonary adenomas were found.

__II.A.4. Supporting Data for Carcinogenicity

Dichloromethane was mutagenic for Salmonella typhimurium with or without the addition of hepatic enzymes (Green, 1983) and produced mitotic recombination in yeast (Callen et al., 1980). Results in cultured mammalian cells have generally been negative, but dichloromethane has been shown to transform rat embryo cells and to enhance viral transformation of Syrian hamster embryo cells (Price et al., 1978; Hatch et al., 1983). Although chlorinated solvents have often been suspected of acting through a nongenotoxic mechanism of cell proliferation, Lefevre and Ashby (1989) found methylene chloride to be unable to induce hepatocellular division in mice.

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_II.B. Quantitative Estimate of Carcinogenic Risk from Oral Exposure

__II.B.1. Summary of Risk Estimates

Oral Slope Factor -- 7.5E-3 per (mg/kg)/day

Drinking Water Unit Risk -- 2.1E-7 per (ug/L)

Extrapolation Method -- Linearized multistage procedure, extra risk

Drinking Water Concentrations at Specified Risk Levels:

Risk Level	Concentration
E-4 (1 in 10,000)	5E+2 ug/L
E-5 (1 in 100,000)	5E+1 ug/L
E-6 (1 in 1,000,000)	5E+0 ug/L

__II.B.2. Dose-Response Data (Carcinogenicity, Oral Exposure)

Tumor Type -- hepatocellular adenomas or carcinomas (NTP) and hepatocellular cancer and neoplastic nodules (NCA)
Test Animals -- mouse/B6C3F1 (female, NTP; male, NCA)
Route -- inhalation (NTP); drinking water (NCA)
Reference -- NTP, 1986; National Coffee Association (NCA), 1983

--------------------Dose--------------------				
Administered		Human Equivalent	Tumor Incidence	Reference
(ppm)	mg/kg/day	(mg/kg)/day		
0	0	0	3/50	NTP, 1986
2000	1582	122	16/48	

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4000	3162	244	40/48	
	0	0	24/125	NCA, 1983
	60	4.5	51/200	
	125	9.4	30/100	
	185	14.0	31/99	
	250	18.9	35/125	

__II.B.3. Additional Comments (Carcinogenicity, Oral Exposure)

The slope factor is an arithmetic mean of slope factors derived from NTP(1986) and the National Coffee Association (1983) data, 2.6E-3 per (mg/kg)/day and 1.2E-2 per (mg/kg)/day, respectively. The use of liver tumor data from the NTP inhalation bioassay was considered valid since dichloromethane is rapidly absorbed following either inhalation or ingestion.

Dose conversions used the mean body weight for female mice at the midpoint of the bioassay, and an estimated inhalation rate of 0.0407 cu.m/day. To obtain estimates of unit risk for humans, an inhalation rate of 20 cu.m/day was assumed. Dichloromethane was considered to be well-absorbed as a vapor at low doses. No pharmacokinetic or metabolism data have been used to modify the oral unit risk estimate, because such analyses have not yet been carried out.

The unit risk should not be used if the water concentration exceeds 5E+4 ug/L, since above this concentration the unit risk may not be appropriate.

__II.B.4. Discussion of Confidence (Carcinogenicity, Oral Exposure)

Adequate numbers of animals were used in both assays. Risk estimates were based on the more sensitive sex in each study. The two risk estimates were within a factor of 5.

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_II.C. Quantitative Estimate of Carcinogenic Risk from Inhalation Exposure

__II.C.1. Summary of Risk Estimates

Inhalation Unit Risk -- 4.7E-7 per (ug/cu.m)

Extrapolation Method -- Linearized multistage procedure, extra risk

Air Concentrations at Specified Risk Levels:

Risk Level	Concentration
E-4 (1 in 10,000)	2E+2 ug/cu.m
E-5 (1 in 100,000)	2E+1 ug/cu.m
E-6 (1 in 1,000,000)	2E+0 ug/cu.m

__II.C.2. Dose-Response Data for Carcinogenicity, Inhalation Exposure

Tumor Type -- combined adenomas and carcinomas

Test Animals -- mouse/B6C3F1, female
Route -- inhalation
Reference -- NTP, 1986

Tumor Type	Administered (ppm)	Transformed Animal (mg/kg)/day	Human Equivalent (mg/kg)/day	Tumor Incidence
	------------Dose		----------------	
Liver	0	0	0	3/45
	2000	1582	356	16/46
	4000	3162	712	40/46
Lung	0	0	0	3/45
	2000	1582	356	30/46
	4000	3162	712	41/46

__II.C.3. Additional Comments (Carcinogenicity, Inhalation Exposure)

The unit risk of 4.7E-7 per (ug/cu.m), which incorporates information on pharmacokinetics and metabolism of dichloromethane, is approximately nine-fold lower than the previous applied dose estimate (U.S. EPA, 1987a,b). Internal dose estimates were based on the metabolism of dichloromethane by the glutathione-s-transferase pathway, as estimated by the model developed by Andersen et al. (1987). The internal dose was corrected for interspecies differences in sensitivity by using the surface area correction factor.

Calculation of a slope factor from the unit risk is inappropriate when pharmacokinetic models are used. (When dose-response relationships are figured on the basis of internal or metabolized dose, a slope factor in terms of per (mg/kg)/day represents a back calculation using different absorption assumptions than the pharmacokinetic models. This introduces possible contradictions.)

The unit risk should not be used if the air concentration exceeds 2E+4 ug/cu.m, since above this concentration the unit risk may differ from that stated. Since the unit risk is based on a pharmacokinetic model, the risk may change with alterations in exposure patterns. Thus, the unit risk presented here may not be applicable to acute, high exposures.

__II.C.4. Discussion of Confidence (Carcinogenicity, Inhalation Exposure)

Adequate numbers of animals were observed and tumor incidences were significantly increased in a dose-dependent fashion. Analysis excluding animals that died before observation of the first tumors produced similar risk estimates, as did time-to-tumor analysis. The use of animal and human metabolism and pharmacokinetic data reduces some of the uncertainty typically associated with dose-risk extrapolation. A great deal of uncertainty still exists, however, in the estimates of internal dose generated by the model of Andersen et al. (1987). Important uncertainties remain regarding the pharmacokinetics, pharmacodynamics, and mechanisms of carcinogenicity for dichloromethane.

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_II.D. EPA Documentation, Review, and Contacts (Carcinogenicity Assessment)

__II.D.1. EPA Documentation

Source Document -- U.S. EPA, 1985a,b, 1987a,b

The Addendum to the Health Assessment Document, the Update to the Health Assessment Document and Addendum, and the Technical Analysis of New Methods and Data for dichloromethane have received Agency and external review, including a review by the Science Advisory Board (SAB). Although the last two documents are not yet finalized and the SAB comments are not yet incorporated, these do not alter this document's analyses or conclusions.

__II.D.2. EPA Review (Carcinogenicity Assessment)

Agency Work Group Review -- 11/12/1986, 12/04/1986, 04/06/1989

Verification Date -- 04/06/1989

Screening-Level Literature Review Findings -- A screening-level review conducted by an EPA contractor of the more recent toxicology literature pertinent to the IUR for Dichloromethane conducted in September 2002 (revised April 2003) identified one or more significant new studies. IRIS users may request the references for those studies from the IRIS Hotline at hotline.iris@epa.gov or (202)566-1676.

__II.D.3. EPA Contacts (Carcinogenicity Assessment)

Please contact the IRIS Hotline for all questions concerning this assessment or IRIS, in general, at (202)566-1676 (phone), (202)566-1749 (FAX) or hotline.iris@epa.gov (internet address).

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_III. [reserved]
_IV. [reserved]
_V. [reserved]

_VI. *Bibliography*

Substance Name -- Dichloromethane
CASRN -- 75-09-2
Primary Synonym -- Methylene Chloride
Last Revised -- 08/01/1991

_VI.A. Oral RfD References

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_VI.B. Inhalation RfC References

None

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_VI.C. Carcinogenicity Assessment References

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_VII. Revision History

Substance Name -- Dichloromethane
CASRN -- 75-09-2
Primary Synonym -- Methylene Chloride

Date	Section	Description
04/20/1987	II.C.1.	Unit Risk corrected from 4.1E-4 to 4.1E-6
05/21/1987	II.A.2.	Missing text replaced in 3rd paragraph
03/01/1988	I.A.1.	Dose conversion clarified
03/01/1988	I.A.2.	Text revised
03/01/1988	II.B.3.	Text revised
03/01/1988	II.B.4.	Confidence statement revised
03/01/1988	II.C.3.	Text revised
03/01/1988	II.C.4.	Confidence statement revised
03/01/1988	II.D.3.	Primary contact changed
03/01/1988	III.A.	Health Advisory added
01/01/1989	II.	Carcinogen summary noted as pending change
10/01/1989	II.B.3.	Inhalation rate corrected in paragraph 1
10/01/1989	II.C.2.	Dose corrections in mg/kg/day
10/01/1989	II.C.3.	Inhalation rate corrected in paragraph 1
10/01/1989	II.D.3.	Contacts phone number changed
08/01/1990	IV.F.1.	EPA contact changed
09/01/1990	II.	Carcinogen assessment revised following re-evaluation
09/01/1990	II.C.1.	Inhalation unit risk changed
09/01/1990	VI.	Bibliography on-line
01/01/1991	II.C.1.	Paragraph moved to II.C.3.
01/01/1991	II.C.1.	Inhalation slope factor removed (global change)
08/01/1991	VI.C.	Citations clarified
09/01/1991	I.B.	Inhalation RfC now under review
01/01/1992	IV.	Regulatory actions updated
02/01/1995	II.D.3.	Primary contact changed
08/01/1995	I.B.	EPA's RfD/RfC and CRAVE workgroups were discontinued in May, 1995. Chemical substance reviews that were not completed by September 1995 were taken out of IRIS review. The IRIS Pilot Program replaced the workgroup functions beginning in September, 1995.
04/01/1997	III., IV., V.	Drinking Water Health Advisories, EPA Regulatory Actions, and Supplementary Data were removed from IRIS on or before April 1997. IRIS users were directed to the appropriate EPA Program Offices for this information.

12/03/2002	I.A.6., II.D.2.	Screening-Level Literature Review Findings message has been added.
04/29/2003	II.D.2.	Screening Level Literature Review findings revised.
07/30/2003	I., II.	This chemical is being reassessed under the IRIS Program.

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_VIII. Synonyms

Substance Name -- Dichloromethane
CASRN -- 75-09-2
Primary Synonym -- Methylene Chloride
Last Revised -- 01/31/1987

75-09-2
Aerothene MM
Chlorure de methylene
DCM
Dichlormethan, uvasol
Dichloromethane
1,1-Dichloromethane.
Freon 30
Methane dichloride
Methane, dichloro-
Methylene bichloride
Methylene Chloride
Methylene dichloride
Metylenu chlorek
Narkotil
NCI-C50102
R 30
Solaesthin
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